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Monte-Carlo Simulation of a Multi-Dimensional Switch-Like Model of Stem Cell Differentiation

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1. Introduction

The process controlling the differentiation of stem, or progenitor, cells into one specific functional direction is called lineage specification. An important characteristic of this process is the multi-lineage priming, which requires the simultaneous expression of lineage-specific genes. Prior to commitment to a certain lineage, it has been observed that these genes exhibit intermediate values of their expression levels. Multi-lineage differentiation has been reported for various progenitor cells (Akashi et al., 2003; Graf, 2002; Hu et al., 1997; Kim et al., 2005; Loose & Patient, 2006; Miyamoto et al., 2002; Patient et al., 2007; Swiers et al., 2006), and it has been explained through the bifurcation of a metastable state (Chickarmane et al., 2009; Huang et al., 2007; Roeder & Glauche, 2006). During the differentiation process the dynamics of the core regulatory network follows a bifurcation, where the metastable state, corresponding to the progenitor cell, is destabilized and the system is forced to choose between the possible developmental alternatives. While this approach gives a reasonable interpretation of the cell fate decision process, it fails to explain the multi-lineage priming characteristic. Here, we describe a new multi-dimensional switch-like model that captures both the process of cell fate decision and the phenomenon of multi-lineage priming. We show that in the symmetrical interaction case, the system exhibits a new type of degenerate bifurcation, characterized by a critical hyperplane, containing an infinite number of critical steady states. This critical hyperplane may be interpreted as the support for the multi-lineage priming states of the progenitor. Also, the cell fate decision (the multi-stability and switching behavior) can be explained by a symmetry breaking in the parameter space of this critical hyperplane. These analytical results are confirmed by Monte-Carlo simulations of the corresponding chemical master equations.

2. Stem cell differentiation

The processes describing the interactions in systems like transcriptional regulatory networks are extremely complex. Genes can be turned on or off by the binding of proteins to regulatory sites on the genome (Ozbundak et al., 2002; Ptashne & Gann, 2002). The proteins are known as transcription factors, while the DNA-binding sites are known as promoters. Transcription factors can regulate the production of other transcription factors, or they can regulate their

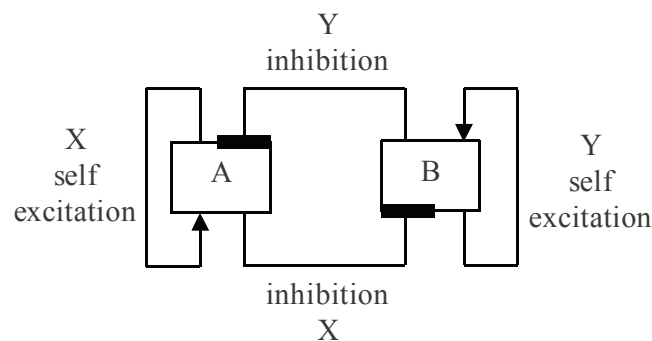


Fig. 1. The architecture of the self-excitation and inhibition mechanisms in the binary cell fate decision circuit.

own production. The transcription process can be described by a sequence of reactions, in which RNA polymerase (R) binds to a gene's promoter leading to the transcription of a complete messenger RNA molecule. The genetic information transcribed into messenger RNA molecules is then translated into proteins by ribosomes. Thus, the general assumption is that the genes can be excited or inhibited by the products of the other genes in the network, generating complex behavior like multi-stability and switching between different steady state attractors. Based on these general assumptions, it has been shown that a simple gene regulatory circuit (Fig. 1) in which two transcription factors, X and Y , inhibit each other, and in the same time activate themselves, can be used as a model of binary cell fate decision in multipotent stem or progenitor cells (Chickarmane et al., 2009; Huang et al., 2007; Roeder & Glauche, 2006). This circuit can generate multistability and explains the symmetric precursor state, in which both factors are present in the cell at equal (low) amounts. This circuit typically produces three stable *attractor* states that correspond to observable cell states. The state 1, with the expression pattern $X \gg Y$, and the state 2, with the opposite pattern $Y \gg X$ represent the cell fates, while the state 3, with a balanced expression $X \simeq Y$ represents the undecided multipotent state. This simple model provides a conceptual framework for understanding cell fate decisions, and it will be used as a starting point in the development of our model.

3. Monte-Carlo simulation approach

The Monte-Carlo simulation approach employed here is based on the well known Gillespie algorithm (Gillespie, 1977), which is a variety of a dynamic Monte Carlo method. The traditional continuous and deterministic description of biochemical rate equations, modeled as a set of coupled ordinary differential equations, relies on bulk reactions that require the interactions of millions of molecules. In contrast, the Gillespie stochastic algorithm simulates every reaction explicitly, and calculates the time evolution of the system by determining the probabilities of each discrete chemical reaction and the resulting changes in the number of each molecular species presented in the system. This algorithm has rigorous theoretical foundations, and gives the exact solution for a system of elementary chemical reactions in the approximation of a well-mixed environment. When simulated, a Gillespie realization represents a random walk that exactly represents the distribution of the chemical master equation. The algorithm is computationally expensive and several modifications have been proposed to speed up computation, including the next reaction method, tau-leaping, as well as hybrid techniques where abundant reactants are modeled with deterministic behavior (Gibson & Bruck, 2000; Rathinam et al., 2003; Slepoy et al., 2008). These adapted techniques

provide a compromise between computational speed and the exactitude of the theory behind the algorithm as it connects to the chemical master equation. Here we use the standard stochastic simulation algorithm, known as the Gillespie's direct method. The rigorous derivation of the algorithm has been given elsewhere and it has been shown to remain "exact" for arbitrary low number of molecules (Gillespie, 1977). Consider a system composed of N chemical species X_v ($v = 1, \dots, N$), interacting through M reactions R_μ ($\mu = 1, \dots, M$) in the cell volume V . Every chemical reaction R_μ is characterized by its stochastic rate constant k_μ , which depends on the physical properties of the molecules taking part in the reaction. The product $k_\mu dt$ is the probability that one elementary reaction R_μ happens in the next infinitesimal time interval dt . The main steps of the Gillespie algorithm consist of:

- (a) calculating the waiting time τ for the next reaction to occur;
- (b) determining which reaction μ in the system actually will occur.

These quantities are computed by generating two random numbers according to the following probability density function:

$$P(\tau, \mu) = a_\mu \exp(-a_0 \tau),$$

(1)

where

$$a_\mu = m_\mu k_\mu,$$

(2)

and

$$a_0 = \sum_{\mu=1}^M a_\mu.$$

(3)

Here, m_μ is the number of distinct reactant combinations available for the reaction R_μ at the given state of the system. The coefficient a_μ is called the propensity of reaction R_μ . Thus, $P(\tau, \mu)$ is the probability that the next reaction will occur in the infinitesimal time interval dt and that it will be the R_μ reaction. After determination of τ and μ , the numbers of molecules in the system are adjusted according to the reaction R_μ . Also, the time t is advanced to $t + \tau$. The larger the propensity is, the greater is the chance that a given reaction will happen in the next step of the simulation. It is worth noting that there is no constant length for a time-step in the simulation. The length of each time-step is determined independently in every iteration, and takes different values depending on the state of the system.

The implementation of the Gillespie algorithm is straightforward, and one can find excellent descriptions of it in the literature (Adalsteinsson et al., 2004; Kierzek, 2002). Below we give the pseudo-code of the algorithm:

#Gillespie's direct method

- 1. Set initial numbers of molecules, set time $t \leftarrow 0$;
- 2. Calculate the propensities, a_μ , for all $\mu = 1, \dots, M$;
- 3. Choose μ with the probability:

$$\Pr(\text{reaction} = \mu) = \frac{a_\mu}{\sum_{\mu=1}^M a_\mu};$$

(4)

- 4. Choose τ with the probability:

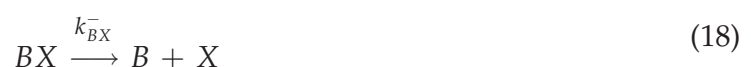
$$\Pr(\text{time} = \tau) = \left(\sum_{\mu=1}^M a_\mu\right) \exp\left[-\tau \left(\sum_{\mu=1}^M a_\mu\right)\right];$$

(5)

5. Change the number of molecules to reflect execution of reaction μ ;
6. Set $t \leftarrow t + \tau$, and go to step 2.

4. 2-Dimensional model

We consider the two gene circuit shown in Figure 1. We will focus on the elementary processes that must occur, such as the promoter binding of the transcription factors X and Y to the promoters, A and B , respectively, and the activation and degradation of transcription factors. Also, we propose a general approach to integrate the two inputs to each gene, which does not depend on the assumption of cooperativity or other explicit modeling. In order to provide a quantitative model of this genetic circuit, we employ a formalism originally developed for the mean-field description of the stochastic interactions in transcriptional regulatory networks (Andrecut & Kauffman, 2006; Andrecut et al., 2008). The promoter binding and unbinding, subsequent self-activation, inhibition, dissociation and the degradation reactions for X , and respectively Y , are:





Here, k_{AX}^+ , k_{AX}^- , k_{BY}^+ , k_{BY}^- , describe the binding and release rates between the transcription factor and the promoter element, k_{AY}^+ , k_{AY}^- , k_{BX}^+ , k_{BX}^- correspond to the cross inhibition rates, while k_X^+ , k_X^- , k_Y^+ , k_Y^- reflect the activation and the degradation rates of the transcription factors. We assume that the role of the first reaction for each transcription factor, Equation 6 and respectively Equation 13, is just to provide a small "basic level of expression" (with the rates k_{AR} , and respectively k_{BR}), in order to avoid their complete extinction. It's effect is equivalent to a positive noise term $\eta_{X,Y}$ in the differential equation describing the dynamics of the transcription factor. Therefore, in the following analysis we will neglect the contribution of this reaction, since it doesn't really have an influence on the "logic functionality" of the circuit. The dynamical behavior (rate of change of active levels of the proteins) of the isolated transcription factors is therefore described by the stochastic differential equations:

$$\frac{d}{dt}[X] = k_X^+[AX] - k_X^-[X] + \eta_X, \quad (20)$$

$$\frac{d}{dt}[Y] = k_Y^+[BY] - k_Y^-[Y] + \eta_Y, \quad (21)$$

where $[.]$ denotes concentration. Assuming that the reversible binding-unbinding processes are in equilibrium, we have:

$$k_{AX}[A][X] = [AX], \quad (22)$$

$$k_{BY}[B][Y] = [BY], \quad (23)$$

$$k_{AY}[A][Y] = [AY], \quad (24)$$

$$k_{BX}[B][X] = [BX], \quad (25)$$

where $k_{AX} = k_{AX}^-/k_{AX}^+$, $k_{BY} = k_{BY}^-/k_{BY}^+$, $k_{AY} = k_{AY}^-/k_{AY}^+$, $k_{BX} = k_{BX}^-/k_{BX}^+$. Also, since the promoters can be in three different states we have:

$$[AX] + [AY] + [A] = [A_0], \quad (26)$$

$$[BY] + [BX] + [B] = [B_0], \quad (27)$$

where $[A_0]$ and $[B_0]$ are the total concentrations of the two promoters. From the above equations, and neglecting the noise terms, we obtain the following system of deterministic differential equations:

$$\frac{d}{dt}x = \alpha x \left(\frac{a_3}{a_1 x + a_2 y + 1} - 1 \right), \quad (28)$$

$$\frac{d}{dt}y = \beta y \left(\frac{b_3}{b_1 x + b_2 y + 1} - 1 \right), \quad (29)$$

where we assumed that: $x = [X]$, $y = [Y]$, $\alpha = k_X^-$, $\beta = k_Y^-$, $a_1 = k_{AX}$, $b_1 = k_{BX}$, $a_2 = k_{AY}$, $b_2 = k_{BY}$, $a_3 = [A_0]k_{AX}k_X^+/k_X^-$, $b_3 = [B_0]k_{BY}k_Y^+/k_Y^-$.

We are interested in the symmetrical case, where $\alpha = \beta$, $a_1 = b_2$, $a_2 = b_1$, $a_3 = b_3$, such that the system becomes:

$$\frac{d}{dt}x = \alpha x \left(\frac{a_3}{a_1 x + a_2 y + 1} - 1 \right), \quad (30)$$

$$\frac{d}{dt}y = \alpha y \left(\frac{a_3}{a_2 x + a_1 y + 1} - 1 \right). \quad (31)$$

The steady states of the above differential system of equations are given by the solutions of the non-linear system:

$$\frac{d}{dt}x = 0 \Leftrightarrow F(x, y, \alpha, \{a\}) = \alpha x \left(\frac{a_3}{a_1 x + a_2 y + 1} - 1 \right) = 0, \quad (32)$$

$$\frac{d}{dt}y = 0 \Leftrightarrow G(x, y, \alpha, \{a\}) = \alpha y \left(\frac{a_3}{a_2 x + a_1 y + 1} - 1 \right) = 0. \quad (33)$$

In this case, one can easily verify that the system has four steady states:

$$(x_0, y_0) = (0, 0), \quad (34)$$

$$(x_1, y_1) = \left(\frac{a_3 - 1}{a_1}, 0 \right), \quad (35)$$

$$(x_2, y_2) = \left(0, \frac{a_3 - 1}{a_1} \right), \quad (36)$$

$$(x_3, y_3) = \frac{1}{a_1 + a_2} (a_3 - 1, a_3 - 1), \quad (37)$$

corresponding to the extinction, exclusive and coexistence equilibria. These fixed points are positively defined if $a_3 > 1$.

In order to evaluate the local stability we calculate the eigenvalues, λ and μ , of the Jacobian matrix at these steady states:

$$J(x, y, \alpha, \{a\}) = \begin{bmatrix} \frac{\partial F}{\partial x} & \frac{\partial F}{\partial y} \\ \frac{\partial G}{\partial x} & \frac{\partial G}{\partial y} \end{bmatrix} = \alpha \begin{bmatrix} \frac{a_3(a_2 y + 1)}{(a_1 x + a_2 y + 1)^2} - 1 & -\frac{a_3 a_2 x}{(a_1 x + a_2 y + 1)^2} \\ -\frac{a_3 a_2 y}{(a_2 x + a_1 y + 1)^2} & \frac{a_3(a_2 x + 1)}{(a_2 x + a_1 y + 1)^2} - 1 \end{bmatrix}. \quad (38)$$

The eigenvalues of the Jacobian for the extinction state (x_0, y_0) are:

$$\lambda = \alpha(a_3 - 1) > 0, \quad (39)$$

$$\mu = \alpha(a_3 - 1) > 0. \quad (40)$$

Thus, this steady state is always unstable, since $a_3 > 1$. The eigenvalues for the exclusive steady states, (x_1, y_1) and (x_2, y_2) , are:

$$\lambda = -\alpha \frac{a_3 - 1}{a_3}, \quad (41)$$

$$\mu = -\alpha \frac{(a_3 - 1)(a_2 - a_1)}{a_1 + a_2(a_3 - 1)}, \quad (42)$$

and respectively:

$$\lambda = -\alpha \frac{(a_3 - 1)(a_2 - a_1)}{a_1 + a_2(a_3 - 1)}, \quad (43)$$

$$\mu = -\alpha \frac{a_3 - 1}{a_3}. \quad (44)$$

Therefore, the exclusive equilibria are stable if $a_2 > a_1$, and unstable if $a_2 < a_1$. In contrast, the eigenvalues for the coexistence equilibrium (x_3, y_3) are:

$$\lambda = -\alpha \frac{(a_3 - 1)(a_1 + a_2)}{a_3(a_1 + a_2)}, \quad (45)$$

$$\mu = -\alpha \frac{(a_3 - 1)(a_1 - a_2)}{a_3(a_1 + a_2)}. \quad (46)$$

Since $\lambda < 0$, this steady state is stable if $\mu < 0$, and it loses stability if $\mu > 0$. One can easily see that the stability condition, $\mu < 0$, is equivalent to $a_2 < a_1$. Thus, a change in the ratio $\rho = a_1/a_2$, triggers a bifurcation from one stable steady state (x_3, y_3) , when $\rho < 1$, to two stable steady states (x_1, y_1) and (x_2, y_2) , when $\rho > 1$.

In Fig. 2 and Fig. 3 we give the results of the Monte-Carlo simulations. The initial concentrations and the main reaction constants are set as: $R = 100$, $A_0 = B_0 = 1$, $X_0 = Y_0 = 0$, $k_X^- = k_Y^- = 0.01$, $k_A = k_B = 0.01$, $k_X^+ = k_Y^+ = 0.01$, $k_{AX}^+ = k_{BY}^+ = 1$, $k_{AY}^+ = k_{BX}^+ = 1$. Fig. 2 gives the trajectories $x(t) = X(t)/R$ and $y(t) = Y(t)/R$ for $\rho < 1$, when there is one noisy attractor, corresponding to the coexistence equilibrium, (x_3, y_3) (Fig. 2(a)), and for $\rho > 1$, when there are two noisy attractors, corresponding to the exclusive equilibria, (x_1, y_1) and (x_2, y_2) (Fig. 2(b)). Also, in Fig. 3 we have represented graphically the probability density distribution, $P(x, y)$, of the transcription factors (obtained by averaging over $M = 10^4$ trajectories with $T = 10^7$ reactions events). One can see that for $\rho < 1$, the system has only one noisy attractor, corresponding to the stable fixed point (x_3, y_3) (Fig. 3(a), $a_1 = 1$, $a_2 = 2$), while for $\rho > 1$, the system exhibits two noisy attractors corresponding to the stable fixed points (x_1, y_1) , and respectively (x_2, y_2) (Fig. 3(b), $a_1 = 2$, $a_2 = 1$). We should note that the absolute values of the rate constants do not play a critical role in the simulation, as long as their ratios satisfy the bifurcation constraints.

An important case of the above analysis corresponds to the critical bifurcation parameter $\rho = 1$. In this case the system has the form:

$$\frac{d}{dt}x = \alpha x \Phi(x, y, \{a\}), \quad (47)$$

$$\frac{d}{dt}y = \alpha y \Phi(x, y, \{a\}), \quad (48)$$

where

$$\Phi(x, y, \{a\}) = \frac{a_3}{a_1(x + y) + 1} - 1. \quad (49)$$

One can easily verify that in this case, the exclusive and coexistence equilibria disappear, and the system has an infinite number of steady states $\Omega = \{(x, y) \in \mathbb{R}^2 | \Phi(x, y, \{a\}) = 0\}$, which are practically equivalent to the positive segment of the linear equation: $x + y = (a_3 - 1)/a_1$. These steady states have the following eigenvalues:

$$\lambda = 0, \quad (50)$$

$$\mu = -(a_3 - 1)/a_3 < 0. \quad (51)$$

Therefore, the steady states Ω are stable, and the system undergoes a degenerate bifurcation (see Appendix). This situation is presented in Fig. 2(c) and Fig. 3(c), for $a_1 = a_2 = 1$. One can see that the stochastic system is "undecided", exploring every point of the critical line with non-zero probability. The line is attracting, except along itself, that is, there is no "longitudinal" force on this line. Therefore every state on it is indifferently stable. Thus, the critical line becomes an ergodic attractor.

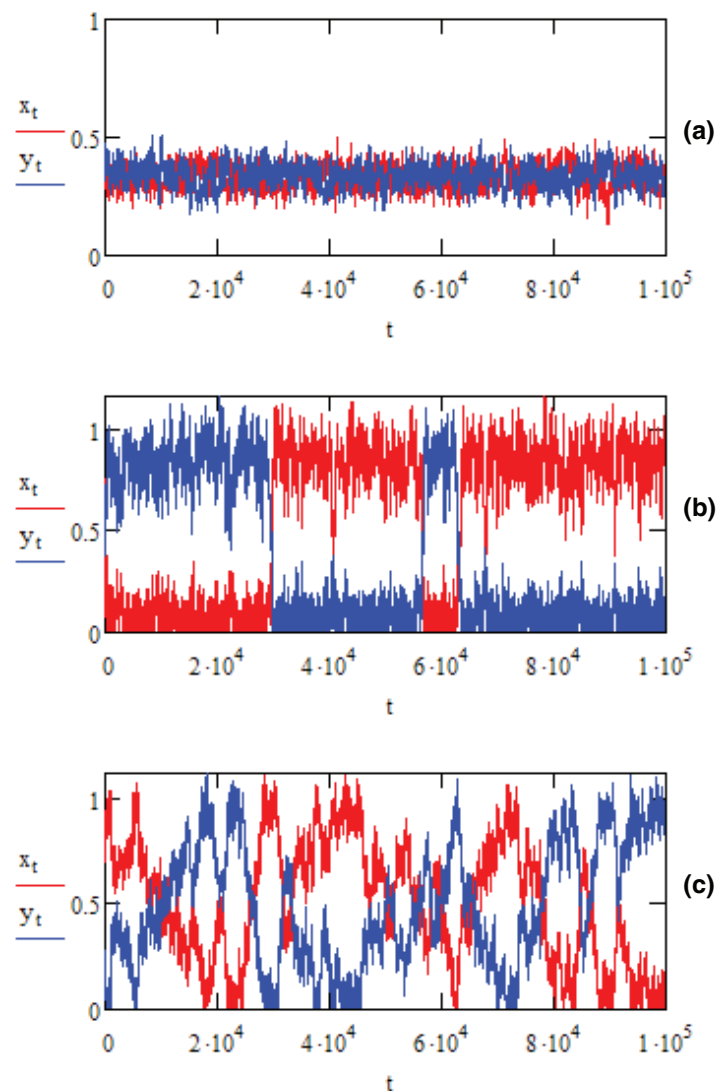


Fig. 2. Monte-Carlo simulation of the 2-dimensional circuit: (a) $\rho < 1$, one attractor ($k_{AX}^- = k_{BY}^- = 0.5$ and $k_{AY}^- = k_{BX}^- = 1$); (b) $\rho > 1$, two attractors ($k_{AX}^- = k_{BY}^- = 1$ and $k_{AY}^- = k_{BX}^- = 0.5$); (c) $\rho = 1$, the critical case of the degenerate bifurcation ($k_{AX}^- = k_{BY}^- = k_{AY}^- = k_{BX}^- = 1$).

5. N-Dimensional model

We consider a N -gene circuit, where we denote by X_n the transcription factors and by A_n the promoters, $n = 1, \dots, N$. For each gene we assume the following set of equations:



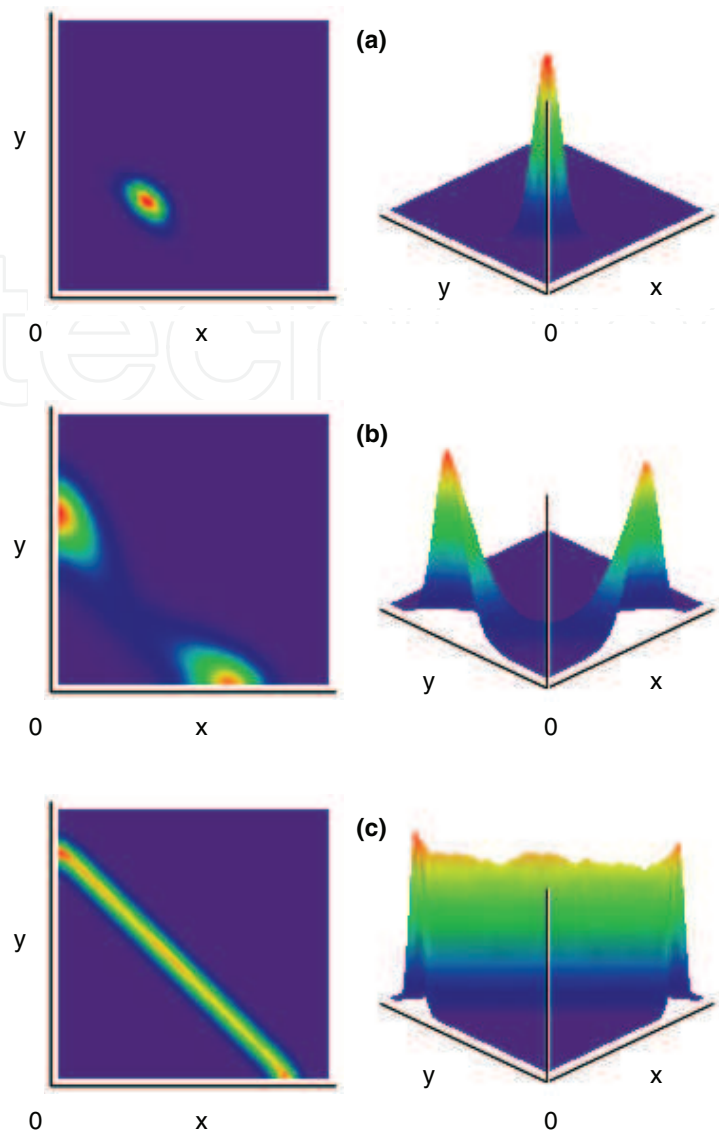
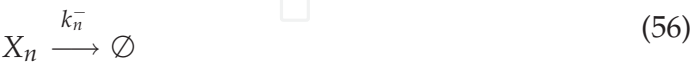
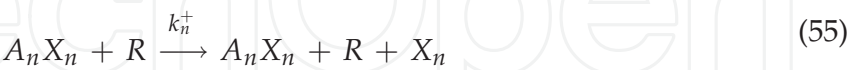


Fig. 3. The probability density distribution, $P(x, y)$, of the stochastic trajectory of the 2-dimensional circuit: (a) $\rho < 1$, one attractor; (b) $\rho > 1$, two attractors; (c) $\rho = 1$, the critical case of the degenerate bifurcation.



Thus, the promoter A_n can bind to any of the N transcription factors. Therefore, the dynamical behavior of the transcription factors is described by the following system of stochastic differential equations:

$$\frac{d}{dt}[X_n] = k_n^+[A_nX_n] - k_n^-[X_n] + \eta_{X_n}, \quad n = 1, \dots, N, \tag{57}$$

where η_{X_n} is the noise term corresponding to the first reaction (52). Assuming that the reversible binding-unbinding processes are in equilibrium, we have:

$$k_{nm}[A_n][X_m] = [A_nX_m], \quad n, m = 1, \dots, N, \quad (58)$$

where $k_{nm} = k_{nm}^-/k_{nm}^+$. Also, since the promoters can be in $N + 1$ different states we have:

$$\sum_{m=1}^N [A_nX_m] + [A_n] = [A_n^0], \quad n = 1, \dots, N. \quad (59)$$

where $[A_n^0]$ are the total concentrations of the promoters. From the above equations, and neglecting the noise terms, we obtain the following system of deterministic differential equations:

$$\frac{d}{dt}x_n = \alpha_n x_n \left(\frac{\beta_n k_{nn}}{\sum_{m=1}^N k_{nm} x_m + 1} - 1 \right), \quad n = 1, \dots, N. \quad (60)$$

where we assumed that: $x = [X_n]$, $\alpha_n = k_n^-$, $\beta_n = [A_n^0]k_n^+/k_n^-$.

Let us consider now the symmetric case:

$$\frac{d}{dt}x_n = F_n(x_1, \dots, x_N, \alpha, \beta, \kappa, \gamma) = \alpha x_n \left(\frac{\beta \kappa}{\kappa x_n + \gamma \sum_{m \neq n} x_m + 1} - 1 \right), \quad n = 1, \dots, N, \quad (61)$$

where $\kappa = k_{nn}$ and $\gamma = k_{nm}$ for $m \neq n = 1, \dots, N$. The steady states corresponds to the solutions of the nonlinear system:

$$\frac{d}{dt}x_n = 0 \Leftrightarrow F_n(x_1, \dots, x_N, \alpha, \beta, \kappa, \gamma) = 0, \quad n = 1, \dots, N. \quad (62)$$

There are $N + 2$ steady states:

$$(x_1^{(0)}, \dots, x_N^{(0)}) = (0, \dots, 0), \quad (63)$$

$$(x_1^{(i)}, \dots, x_n^{(i)}, \dots, x_N^{(i)}) = \left(0, \dots, \frac{\beta \kappa - 1}{\kappa}, \dots, 0 \right), \quad i = 1, \dots, N, \quad (64)$$

$$(x_1^{(N+1)}, \dots, x_N^{(N+1)}) = \left(\frac{\beta \kappa - 1}{\kappa + (N-1)\gamma}, \dots, \frac{\beta \kappa - 1}{\kappa + (N-1)\gamma} \right). \quad (65)$$

Again, these states correspond to extinction, N -exclusive and coexisting equilibria, and they are positively defined if $\beta \kappa > 1$. The stability of these states can be analyzed using the eigenvalues of the Jacobian matrix:

$$J(x_1, \dots, x_N, \alpha, \beta, \kappa, \gamma) = \left[\frac{\partial}{\partial x_i} F_n(x_1, \dots, x_N, \alpha, \beta, \kappa, \gamma) \right]_{n,i=1, \dots, N}, \quad (66)$$

where

$$\frac{\partial}{\partial x_i} F_n = \begin{cases} \frac{\alpha \beta \kappa (\gamma \sum_{m \neq n} x_m + 1)}{(\kappa x_n + \gamma \sum_{m \neq n} x_m + 1)^2} - \alpha & \text{if } n = i \\ -\frac{\alpha \beta \kappa \gamma x_n}{(\kappa x_n + \gamma \sum_{m \neq n} x_m + 1)^2} & \text{if } n \neq i \end{cases}. \quad (67)$$

The eigenvalues of the extinction state are:

$$\lambda_n = \alpha (\beta \kappa - 1), \quad n = 1, \dots, N, \quad (68)$$

which means that this steady state is always unstable, since $\beta\kappa > 1$. For the exclusive equilibria the eigenvalues are:

$$\lambda_n = \begin{cases} -\frac{\alpha(\beta\kappa-1)}{\beta\kappa} & \text{if } n = i \\ -\frac{\alpha(\beta\kappa-1)(\gamma-\kappa)}{\gamma(\beta\kappa-1)+\kappa} & \text{if } n \neq i \end{cases}, \quad n = 1, \dots, N. \quad (69)$$

Therefore, these states become stable if $\gamma > \kappa$, and unstable if $\gamma < \kappa$. In the case of coexisting equilibrium the Jacobian is given by:

$$\frac{\partial}{\partial x_i} F_n = \begin{cases} \frac{\alpha(1-\beta\kappa)}{\beta[\kappa+(N-1)\gamma]} & \text{if } n = i \\ -\frac{\alpha\gamma(\beta\kappa-1)}{\beta k[\kappa+(N-1)\gamma]} & \text{if } n \neq i \end{cases}, \quad (70)$$

and it has the following eigenvalues:

$$\lambda_n = \begin{cases} -\frac{\alpha(\beta\kappa-1)}{\beta\kappa} & \text{if } n = i \\ -\frac{\alpha(\beta\kappa-1)(\kappa-\gamma)}{\beta k[\kappa+(N-1)\gamma]} & \text{if } n \neq i \end{cases}, \quad n = 1, \dots, N. \quad (71)$$

Thus, this state becomes stable if $\gamma < \kappa$, and unstable if $\gamma > \kappa$.

In the critical case, $\kappa = \gamma$, the steady state equations are degenerated and we have again an infinite number of steady states, all of them satisfying the critical hyperplane equation:

$$\sum_{n=1}^N x_n = \frac{\beta\kappa-1}{\kappa}. \quad (72)$$

In this critical case the Jacobian takes the simplified form:

$$\frac{\partial}{\partial x_i} F_n = -\frac{\alpha}{\beta} x_n, \quad (73)$$

and it has the following eigenvalues:

$$\lambda_n = \begin{cases} -\frac{\alpha(\beta\kappa-1)}{\beta\kappa} & \text{if } n = i \\ 0 & \text{if } n \neq i \end{cases}, \quad n = 1, \dots, N. \quad (74)$$

Thus, one eigenvalue is always negative, since $\beta\kappa > 1$, and the other $N-1$ eigenvalues are zero. Therefore, the hyperplane containing the infinite number of steady states is attractive and marginally stable.

In Fig. 4 we give the simulation results for a circuit consisting of three genes, $N = 3$. The initial concentrations are set as $R = 150$, $A_1 = A_2 = A_3 = 1$, $X_1 = X_2 = X_3 = 0$. The rate constants are the same as for the 2-dimensional circuit. Fig. 4 gives the trajectories $x_n(t)$ for $\gamma < \kappa$, when there is one noisy attractor, corresponding to the coexistence equilibrium, $(x_1^{(3)}, x_2^{(3)}, x_3^{(3)})$ (Fig. 4(a)), and for $\gamma > \kappa$, when there are three noisy attractors, corresponding to the exclusive equilibria, $(x_1^{(1)}, x_2^{(1)}, x_3^{(1)}) = \left(\frac{\beta\kappa-1}{\kappa}, 0, 0\right)$, $(x_1^{(2)}, x_2^{(2)}, x_3^{(2)}) = \left(0, \frac{\beta\kappa-1}{\kappa}, 0\right)$ and $(x_1^{(3)}, x_2^{(3)}, x_3^{(3)}) = \left(0, 0, \frac{\beta\kappa-1}{\kappa}\right)$ (Fig. 4(b)), and in the degenerate case when the plane $x_1 + x_2 + x_3 = \frac{\beta\kappa-1}{\kappa}$ is the ergodic attractor (Fig. 4(c)).

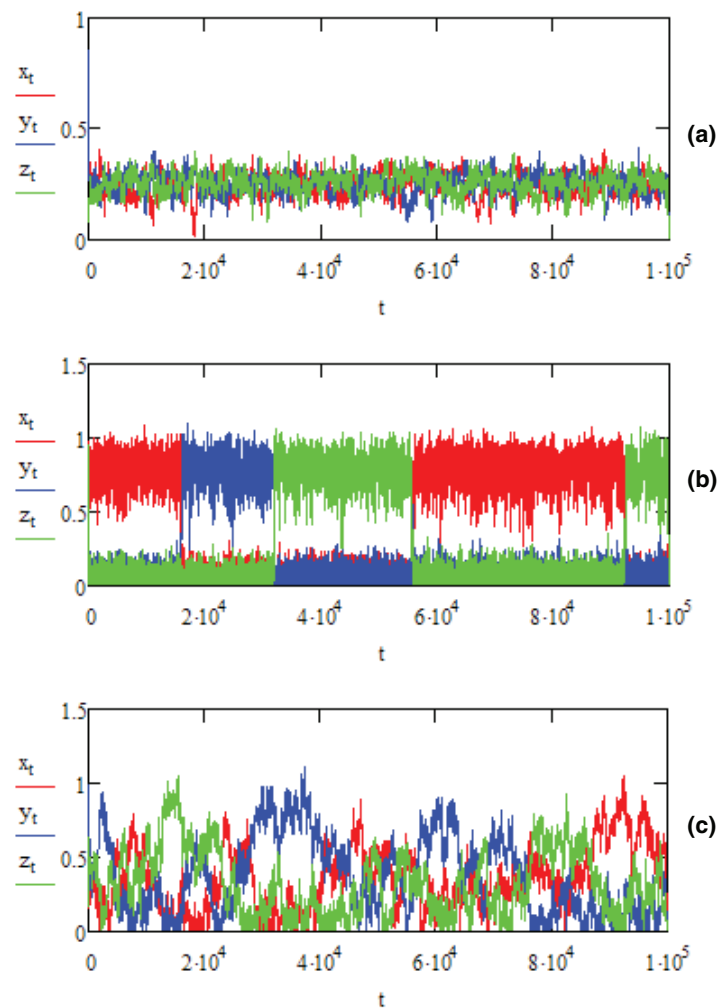


Fig. 4. Monte-Carlo simulation of the 3-dimensional circuit: (a) $\gamma < \kappa$, one attractor; (b) $\gamma > \kappa$, three attractors; (c) $\gamma = \kappa$, the critical case of the degenerate bifurcation.

6. Conclusion

We have presented a new multi-dimensional switch-like model that captures both the process of cell fate decision and the phenomenon of multi-lineage priming. The previous attempts to model the coexistence of three discrete stable states are based on a complicated molecular interaction mechanisms, requiring cooperativity or additional transcription factors (Chickarmane et al., 2009; Huang et al., 2007; Roeder & Glauche, 2006). Here, we have shown that very elementary cross-inhibition between two genes and independent autoactivation can give rise to multistability without cooperativity. It is important to note the obvious fact that the real molecular mechanisms that govern the dynamics of this gene regulatory circuit are by orders of magnitudes more complex, involving perhaps thousands of steps not accounted for in the presented model. However, this simplified description is still able to capture to qualitative cell fate decision behavior, specifically, the existence of an indeterminate multi-potent progenitor state with equal levels of transcription factors, and the generation of stable attractor states with asymmetric expression patterns. Also, we have shown that in the symmetrical interaction case, the system exhibits a new type of degenerate bifurcation, characterized by a critical hyperplane containing an infinite number of critical steady states.

This degeneration of the central attractor state captures the intrinsic heterogeneity of the undecided multipotent state allowing individual cells to a range of states, and may be interpreted as the support for the multi-lineage priming states of the progenitor. Also, the cell fate decision (the multi-stability and switching behavior) can be explained by a symmetry breaking in the parameter space of this critical hyperplane. It is important to note here that the critical hyperplane is also ergodic. Thus, in the critical regime, any stochastic trajectory of the system will be attracted to the critical hyperplane. Also, in this case, the dynamics will become confined to this region, such that the system will visit all the points of the critical hyperplane with non-zero probability (the priming phenomenon). However, any perturbation of this critical hyperplane will force the system to collapse in one of its non-trivial stable steady states (the cell fate decision process).

7. Appendix: Degenerate steady state bifurcation

We consider a 2-dimensional system of stochastic differential equations (SDE), of the following generic form:

$$(S) \quad \begin{cases} \dot{x} = \alpha(\bar{x} - x)\Phi(x, y, \{\gamma\})f(x, y, \{a\}) + \eta_x \\ \dot{y} = \beta(\bar{y} - y)\Phi(x, y, \{\gamma\})g(x, y, \{b\}) + \eta_y \end{cases} \quad (75)$$

where $\Phi, f, g : \mathbb{R}^2 \rightarrow \mathbb{R}$, $x, y, \bar{x}, \bar{y}, \alpha, \beta, \{\gamma\}, \{a\}, \{b\} \in \mathbb{R}$, and η_x, η_y correspond to additive noise terms. Also, we denote by $\Omega = \{(x, y) \in \mathbb{R}^2 | \Phi(x, y, \{\gamma\}) = 0\}$ the set of solutions of the equation $\Phi = 0$, and we assume that: $f(x, y, \{a\}) \neq 0$ and $g(x, y, \{b\}) \neq 0$, for any $(x, y) \in \mathbb{R}^2$.

Theorem 1: The SDE system (S) exhibits a degenerate bifurcation, $(\bar{x}, \bar{y}) \rightarrow \tilde{\Omega} \subset \Omega$, from one steady state (\bar{x}, \bar{y}) to a subset of steady states $\tilde{\Omega} \subset \Omega$, if:

$$\max\{-\alpha\Phi(\bar{x}, \bar{y}, \{\gamma\})f(\bar{x}, \bar{y}, \{a\}), -\beta\Phi(\bar{x}, \bar{y}, \{\gamma\})g(\bar{x}, \bar{y}, \{b\})\} > 0, \quad (76)$$

and

$$\nabla_v \Phi(x, y, \{\gamma\}) = \langle v, \nabla \Phi(x, y, \{\gamma\}) \rangle < 0, \quad (77)$$

for any $(x, y) \in \tilde{\Omega}$ and

$$v = [\alpha(\bar{x} - x)f(x, y, \{a\}), \beta(\bar{y} - y)g(x, y, \{b\})]^T. \quad (78)$$

Proof: A first steady state of the system (S) is (\bar{x}, \bar{y}) . Also the system has an infinite number of steady states Ω , corresponding to the solutions of the equation $\Phi(x, y, \{\gamma\}) = 0$. The stability of the steady states can be analyzed using the eigenvalues, λ_0 and λ_1 , of the Jacobian matrix J , which are given by the solutions of the equation $|J - \lambda I| = 0$, where I is the identity matrix. In general, the eigenvalues are complex numbers, and the distance between the solution of the system and the steady state changes at an exponential rate, given by the real part of the eigenvalue. For simplicity the following discussion is restricted to real eigenvalues, though steady states with complex eigenvalues have similar properties based on the value of the real part of the eigenvalue. A negative eigenvalue implies that the solution approaches the steady state along the corresponding eigenvector, while a positive eigenvalue implies that the solution moves away from the steady state along the eigenvector. In a 2-dimensional system there are three possible cases. A stable steady state has two negative eigenvalues, and hence attracts all the solutions in a surrounding region. An unstable steady state has two positive eigenvalues and all the solutions in its neighborhood move away from it. A saddle point has

one negative and one positive eigenvalue. Now let us analyze the stability of the steady states of the system. The eigenvalues of the Jacobian for (\bar{x}, \bar{y}) are:

$$\begin{cases} \lambda_0 = -\alpha f(\bar{x}, \bar{y}, \{\gamma\})\Phi(\bar{x}, \bar{y}, \{\gamma\}) \\ \lambda_1 = -\beta g(\bar{x}, \bar{y}, \{b\})\Phi(\bar{x}, \bar{y}, \{\gamma\}) \end{cases} \quad (79)$$

Thus, this steady state is stable if $\lambda_0, \lambda_1 < 0$, and it loses stability if $\lambda_0 > 0$ or $\lambda_1 > 0$, which is equivalent to the condition imposed by the Equation 76. The other steady states $(x, y) \in \Omega$, have the following eigenvalues:

$$\begin{cases} \lambda_0 = 0 \\ \lambda_1 = \alpha(\bar{x} - x)f\frac{\partial\Phi}{\partial x} + \beta(\bar{y} - y)g\frac{\partial\Phi}{\partial y} \end{cases} \quad (80)$$

and they are degenerated, since they have at least one zero eigenvalue. Also, these degenerate steady states become stable for $\lambda_1 < 0$. Since $\lambda_1 = \langle v, \nabla\Phi \rangle = \nabla_v\Phi$, this stability condition is equivalent to the condition imposed by the Equation 77, which requires that the derivative of Φ in direction v must be negative. The directional derivative of a manifold Φ along a vector v at a given point (x, y) , intuitively represents the instantaneous rate of change of the manifold, moving through (x, y) , in the direction of v . One can easily verify that in this case, v is the eigenvector of the Jacobian corresponding to the eigenvalue λ_1 , that is we have: $Jv = \lambda_1 v$. Thus, any change in the parameters $\{\gamma\}$, such that the stable steady state (\bar{x}, \bar{y}) becomes unstable, and the steady states $\tilde{\Omega} = \{(x, y) \in \Omega | \nabla_v\Phi(x, y, \{\gamma\}) < 0\}$ become stable, results in a degenerate bifurcation of the dynamics of the stochastic system (S).

A similar property can be formulated for stochastic discrete maps (SDM) of the following generic form:

$$(M) \begin{cases} x_{t+1} = (x_t - \bar{x})[1 - \alpha\Phi(x_t, y_t, \{\gamma\})f(x_t, y_t, \{a\})] + \bar{x} + \eta_x \\ y_{t+1} = (y_t - \bar{y})[1 - \beta\Phi(x_t, y_t, \{\gamma\})g(x_t, y_t, \{b\})] + \bar{y} + \eta_y \end{cases} \quad (81)$$

where $\Phi, f, g : \mathbb{R}^2 \rightarrow \mathbb{R}$, $x_t, y_t, \bar{x}, \bar{y}, \alpha, \beta, \{\gamma\}, \{a\}, \{b\} \in \mathbb{R}$, and η_x, η_y correspond to additive noise terms. We denote by $\Omega = \{(x, y) \in \mathbb{R}^2 | \Phi(x, y, \{\gamma\}) = 0\}$ the set of solutions of the equation $\Phi = 0$. Also, we assume that: $f(x, y, \{a\}) \neq 0$ and $g(x, y, \{b\}) \neq 0$, for any $(x, y) \in \mathbb{R}^2$.

Theorem 2: The SDM system (M) exhibits a degenerate steady state bifurcation, $(\bar{x}, \bar{y}) \rightarrow \tilde{\Omega} \subset \Omega$, from one steady state (\bar{x}, \bar{y}) to a subset of steady states $\tilde{\Omega} \subset \Omega$, if:

$$\max\{|1 - \alpha\Phi(\bar{x}, \bar{y}, \{\gamma\})f(\bar{x}, \bar{y}, \{a\})|, |1 - \beta\Phi(\bar{x}, \bar{y}, \{\gamma\})g(\bar{x}, \bar{y}, \{b\})|\} > 1, \quad (82)$$

and

$$|1 - \nabla_v\Phi(x, y, \{\gamma\})| < 1, \quad (83)$$

for any $(x, y) \in \tilde{\Omega}$ and

$$v = [\alpha(x - \bar{x})f(x, y, \{a\}), \beta(y - \bar{y})g(x, y, \{b\})]^T. \quad (84)$$

Proof: The steady states of the map (P) are (\bar{x}, \bar{y}) , and the set Ω , corresponding to the solutions of the equation $\Phi(x, y, \{\gamma\}) = 0$. As before, the eigenvalues, λ_0 and λ_1 , are given by the equation $|J - \lambda I| = 0$, where J is the Jacobian of the discrete map (P). In the case of discrete

maps, a stable steady state is characterized by $|\lambda_0| < 1$ and $|\lambda_1| < 1$, while an unstable steady state is characterized by $|\lambda_0| > 1$ or $|\lambda_1| > 1$. The eigenvalues of the Jacobian for (\bar{x}, \bar{y}) are:

$$\begin{cases} \lambda_0 = 1 - \alpha\Phi(\bar{x}, \bar{y}, \{\gamma\})f(\bar{x}, \bar{y}, \{a\}) \\ \lambda_1 = 1 - \beta\Phi(\bar{x}, \bar{y}, \{\gamma\})g(\bar{x}, \bar{y}, \{b\}) \end{cases} \quad (85)$$

Thus, this steady state is stable if $|\lambda_0| < 1$ and $|\lambda_1| < 1$, and it becomes unstable if $|\lambda_0| > 1$ or $|\lambda_1| > 1$, which is equivalent to the condition imposed by the Equation 82. The other steady states Ω , have the following eigenvalues:

$$\begin{cases} \lambda_0 = 1 \\ \lambda_1 = 1 - \alpha(x - \bar{x})f\frac{\partial\Phi}{\partial x} - \beta(y - \bar{y})g\frac{\partial\Phi}{\partial y} \end{cases} \quad (86)$$

and they are degenerated, since they have at least one eigenvalue equal to one. These degenerate steady states become stable for $|\lambda_1| < 1$, which is equivalent to the condition imposed by the Equation 83. Also, one can verify that v is the eigenvector of the Jacobian, corresponding to the eigenvalue λ_1 . Thus, any change in the parameters $\{\gamma\}$, such that the stable steady state (\bar{x}, \bar{y}) becomes unstable, and the steady states $\tilde{\Omega} = \{(x, y) \in \Omega \mid |1 - \nabla_v \Phi(x, y, \{\gamma\})| < 1\}$ become stable, results in a degenerate bifurcation of the dynamics of the stochastic discrete map (M) .

8. References

- Adalsteinsson, D., McMillen, D. & Elston, T. C. (2004). Biochemical network stochastic simulator (BioNetS): software for stochastic modeling of biochemical networks. *BMC Bioinformatics*: 5, 1471-2105.
- Akashi, K., He, X., Chen, J., Iwasaki, H., Niu, C., Steenhard, B., Zhang, J., Haug, J. & Li, L. (2003). Transcriptional accessibility for genes of multiple tissues and hematopoietic lineages is hierarchically controlled during early hematopoiesis. *Blood*: 101, 383-389.
- Andreucut, M. & Kauffman, S.A. (2006). Mean-field model of genetic regulatory networks. *New Journal of Physics*: 8, 148.
- Andreucut, M., Cloud, D. & Kauffman, S. A. (2008). Monte Carlo simulation of a simple gene network yields new evolutionary insights. *Journal of Theoretical Biology*: 250(3), 468-474.
- Chickarmane, V., Enver, T. & Peterson, C. (2009). Computational modeling of the hematopoietic erythroid-myeloid switch reveals insights into cooperativity, priming, and irreversibility. *Plos Computational Biology*: 5(1), e1000268.
- Cross, M. A. & Enver, T. (1997). The lineage commitment of hematopoietic progenitor cells. *Current Opinion in Genetics & Development*: 7, 609-613.
- Gibson, M. A. & Bruck, J. (2000). Efficient Exact Stochastic Simulation of Chemical Systems with Many Species and Many Channels. *Journal of Physical Chemistry: A* 104, 1876-1889.
- Gillespie, D.T. (1977). Exact stochastic simulation of coupled chemical reactions. *Journal of Physical Chemistry*: 81, 2340-2361.
- Graf, T. (2002). Differentiation plasticity of hematopoietic cells. *Blood*: 99, 3089-3101.
- Hu, M., Krause, D., Greaves, M., Sharkis, S., Dexter, M., Heyworth, C. & Enver, T. (1997). Multilineage gene expression precedes commitment in the hematopoietic system. *Genes & Development*: 11, 774-785.

- Huang, S., Guo, T-P, May, G. & Enver, T. (2007). Bifurcation dynamics in lineage commitment in bipotent progenitor cells. *Developmental Biology*: 305, 695-713.
- Kim, C.F., Jackson, E.L., Woolfenden, A.E., Lawrence, S., Babar, I., Vogel, S., Crowley, D., Bronson, R.T. & Jacks, T. (2005). Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell*: 121, 823-835.
- Kierzek, A. (2002). STOCKS: STOChastic kinetic simulations of biochemical systems with Gillespie algorithm. *Bioinformatics*: 18, 470-481.
- Loose, M. & Patient, R. (2006). Global genetic regulatory networks controlling hematopoietic cell fates. *Current Opinion in Hematology*: 13, 229-236.
- Miyamoto, T., Iwasaki, H., Reizis, B., Ye, M., Graf, T., Weissman, I. L. & Akashi, K. (2002). Myeloid or lymphoid promiscuity as a critical step in hematopoietic lineage commitment. *Developmental Cell*: 3, 137-147.
- Ozbundak, E. M., Thattai, M., Kurtser, I., Grossman, A. D. & van Oudenaarden, A. (2002). Regulation of noise in the expression of a single gene. *Nature Genetics*: 31, 69-73.
- Patient, R., Swiers, G. & Loose, M. (2007). Transcriptional networks regulating hematopoietic cell fate decisions. *Current Opinion in Hematology*: 14, 307-314.
- Ptashne, M. & Gann, A. (2002). *Genes and signals*. Cold Spring Harbor Laboratory Press, New York.
- Rathinam, M., Petzold, L. R., Cao, Y. & Gillespie, D. T. (2003). Stiffness in stochastic chemically reacting systems: The implicit tau-leaping method. *Journal of Chemical Physics*: 119 (24), 12784-12794.
- Roeder, I. & Glauche, I. (2006). Towards an understanding of lineage specification in hematopoietic stem cells: a mathematical model for the interaction of transcription factors GATA-1 and PU.1. *Journal of Theoretical Biology*: 241, 852-865.
- Slepoy, A., Thompson, A. P. & Plimpton, S. J. (2008). A constant-time kinetic Monte Carlo algorithm for simulation of large biochemical reaction networks. *Journal of Chemical Physics*: 128 (20), 205101.
- Swiers, G., Patient, R. & Loose, M. (2006). Genetic regulatory networks programming hematopoietic stem cells and erythroid lineage specification. *Developmental Biology*: 294, 525-540.

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